PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluating antibiotic stewardship and healthcare-associated infections surveillance assisted by computer: protocol for an interrupted time series study
AUTHORS	Baudet, Alexandre; AGRINIER, Nelly; CHARMILLON, Alexandre; Pulcini, Céline; LOZNIEWSKI, Alain; AISSA, Nejla; LIZON, Julie; THILLY, Nathalie; DEMORÉ, Béatrice; FLORENTIN, Arnaud

VERSION 1 – REVIEW

REVIEWER	Delory, Tristan Sorbonne Universite
REVIEW RETURNED	21-Oct-2021

GENERAL COMMENTS	Baudet and colleagues aims at conducting an interrupted time series analysis to assess the effect of implementation of a system combining CDSS and ESS, on multiple parameters, including overall use of antibiotics. This novel approach for antimicrobial stewardship and surveillance of healthcare associated infection is quite interesting. Study design is “classic” in the field of antimicrobial stewardship. The authors identified potential challenges for statistical analysis such as effect of additional intervention during the surveyed period. Few suggestions may be made: - The lack of internal control group is clearly understandable. However, is it possible to consider embedding aggregated data from hospitals with similar activities: external control group? - In the statistical analysis, the statistical modelling to be used is not detailed. Poisson regressions will likely be used. For the primary endpoint it may be interesting to record the number patients susceptible to the intervention (CDSS) over time, by removing those under antibiotic therapy from the number of patients per time unit. This may allow to better capture the relative effect of intervention by increasing absolute difference which can be observed for evolution of antibiotic consumption over time. This will also be essential to set an offset in the Poisson regression. - The CDSS/ESS may be not perfect, with its own sensitivity and specificity levels? So one can imagine that a patient will not receive CDSS-based prescription while indicated? Is it possible to conduct statistical analyses on individual-level data to compare patients who received prescription based on CDSS compared to those who did not? - The authors assumes that 12-months before / 12-months after observation period for first analysis is sufficient to account for seasonality. This could be questioned. They then report the willingness to conduct a secondary analysis using 24-month periods of observation. As the implementation date (2021?) of

	intervention is not reported, it is not possible to understand how this will be feasible. Please clarify this point. Will you observe the situation for 24 months, then implement the CDSS/ESS, then observe again…or did you plan to collect retrospective data for the 12-months and the 24-months period before the intervention starting (?) ?

REVIEWER	Laka, Mah The University of Adelaide, School of Public Health
REVIEW RETURNED	19-Nov-2021

GENERAL COMMENTS	Thank you for the opportunity to review the protocol of a study which will assess the impact of CDSS and ESS on facilitating antibiotic stewardship and infection prevention and control activities. This study protocol is interesting providing clear outline of the study plan and analysis. My main concern is how the issue of alert fatigue will be handled in implementation. If excessive alerts are generated by APSS daily and especially during weekends which will be treated the next Monday - will there be a risk that AMS team have overwhelming amount of alerts to review? Secondly, how will it be monitored that APSS recommendations are ignored/over-ridden or resulted in changes in prescriptions? Following are some of the minor concerns regarding this study protocol, which the authors may incorporate in the revised manuscript to improve the study quality: Introduction: A brief description/definition of CDSS and ESS would help readers understand the context of study. For example how ESS maximizes the effectiveness of IPC activities? Objectives: One of the secondary outcomes is assess the safety of CDSS/ESS use on the incidence of certain HCAIs, but its not clear which certain HCAIs and how were they selected? Methods: The qualitative data collection is not sufficiently discussed. How many interviews will be conducted?

REVIEWER	Redding, L. E. Univ Penn
REVIEW RETURNED	03-Dec-2021

GENERAL COMMENTS	This is a well-written manuscript with a comprehensively described protocol for evaluation of a stewardship intervention. I do have some concerns about your implementation date. If the AMS and CDSS interventions were initiated in 2021, that means the year prior will have been 2020 and the year after part of 2021 and 2022. Do you anticipate that the covid pandemic will have altered antibiotic usage patterns and that therefore the pre- and post-years will not be comparable? Several studies (e.g., https://doi.org/10.3390/antibiotics10020182, https://doi.org/10.1017/ice.2020.381, https://doi.org/10.1080/23744235.2020.1839672, https://doi.org/10.1016/S1473-3099(20)30917-8 to name just a

	few) have shown very different patterns of antimicrobial prescribing during the pandemic, especially before vaccines became available. Where in your timeline does the implementation of this intervention fit? And how was the hospital affected by the pandemic? I see that you will consider the impact of the pandemic by eventually performing this analysis over a longer time period (24 months before and after), but you may want to say a bit more about whether this is sufficient and discuss how much you think the hospital and antibiotic prescribing may or may not have been affected by the pandemic. Specific comments: P6 L 46: please provide a bit more information on these comparable university hospitals. How many? Where located? Was it a representative sample? P6 L 57-60: Why a random selection? Will the pre- and post-intervention patients be matched in some way? In particular, by indication for antibiotic therapy? If not, how do you ensure comparability? P 9 L 56-60: please provide more information on the interview process beyond “they will be interviewed”. By whom? In what manner? Is there an interview guide you can share? Who will perform the interviews and the analyses? Some clarification on parameters in Table 1 would be appreciated: How do you define an HCAI? “Proportion of the antibiotic prescriptions compliant with guidelines” and “Proportion of the additional precaution prescriptions compliant with hospital recommendations”: will these be evaluated by the software or manually by a person? Proportion of C. difficile. Why do you only consider patients treated with antibiotics? Patients not treated with antibiotics can also develop C. diff infection, especially if immunosuppressed or on gastric acid suppressors, and since it is a hospital-acquired infection often acquired from the hospital environment, you’d hope that the expected decrease in overall AMU associated with your intervention would result in decreased C diff infections in all patients, not just those treated with antibiotics. In fact, you could argue that if your intervention is to decrease AMU overall, you may have some patients who were not treated with antibiotics who previously might have been, and I would think you would want to capture these patients in your denominator. A few small grammatical errors here and there (this is just a sampling, check the manuscript thoroughly). P6 L 53: “Infectious disease physicians also meet daily [with] microbiologists” P 9 L 11 “excepted”

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Dr. Tristan Delory, Sorbonne Universite

Comments to the Author:
Baudet and colleagues aims at conducting an interrupted time series analysis to assess the effect of implementation of a system combining CDSS and ESS, on multiple parameters, including overall use of antibiotics. This novel approach for antimicrobial stewardship and surveillance of healthcare associated infection is quite interesting. Study design is “classic” in the field of antimicrobial stewardship. The authors identified potential challenges for statistical analysis such as effect of additional intervention during the surveyed period.
Dear Dr. Tristan Delory, thank you for the reviewing of our manuscript.

Few suggestions may be made:
- The lack of internal control group is clearly understandable. However, is it possible to consider embedding aggregated data from hospitals with similar activities: external control group?
Interrupted time series (ITS) analysis differs from most other intervention study designs in that it involves a before-after comparison within a single population (the pre-intervention period acts as the control), rather than a comparison with a control group. Although it is interesting to add a control group in certain ITS studies of public health interventions to control confounding events, this control may also be associated with limitations. Indeed, a control group can also introduce new sources of bias to the study, and particularly with an external control group because an ideal control group should be exposed to any such co-interventions or events that might also affect the intervention group. This is not possible with another hospital as control. We referred to: Lopez Bernal J, Cummins S, Gasparrini A. The use of controls in interrupted time series studies of public health interventions. Int J Epidemiol. 2018 01;47(6):2082–93. So, no external control group is planned in our study. We can observe that the majority of the ITS studies performed in hospital settings did not use a control group. We had two sentences in this way in our manuscript.
On the one hand, it is not easy to access the aggregated monthly data from another hospital with similar activities, in particular for practical and regulatory reasons regarding the standard of data protection directives (for example, in our study, the data originated from our hospital must be saved and analyzed only with servers and computers of our hospital).
- In the statistical analysis, the statistical modelling to be used is not detailed. Poisson regressions will likely be used. For the primary endpoint it may be interesting to record the number patients susceptible to the intervention (CDSS) over time, by removing those under antibiotic therapy from the number of patients per time unit. This may allow to better capture the relative effect of intervention by increasing absolute difference which can be observed for evolution of antibiotic consumption over time. This will also be essential to set an offset in the Poisson regression.
We did not detail the statistical model because we need to analyze the distribution of the data before selecting the most appropriate model. We will probably use a Poisson regression, but we need to check that the distribution is in accordance with the Poisson law (in particular: the outcomes are rare events, and variance=mean), and that we can control the seasonality (residual autocorrelation much smaller than in the raw outcome data) because Poisson’s law is violated if the observations are not independent in time.
- The CDSS/ESS may be not perfect, with its own sensitivity and specificity levels? So one can imagine that a patient will not receive CDSS-based prescription while indicated? Is it possible to conduct statistical analyses on individual-level data to compare patients who received prescription based on CDSS compared to those who did not?
Analysis of sensitivity and specificity are not planned in this study. The period during which the CDSS/ESS is installed and during which the healthcare users trained should allow problems to be identified (AMS/IPC teams will compare patients manually reviewed to those identified by the

CDSS/ESS) and any necessary changes to critical systems to be implemented before the start of the intervention.
On the other hand, one of the secondary objectives is to assess the proportion of the antibiotic/additional precaution prescriptions compliant with guidelines/hospital recommendations. This assessment will allow highlighting if patients have not received CDSS-based prescription while indicated. Finally, the “false positive” alerts generated by CDSS will be numbered for another secondary objective: calculation of the proportion of CDSS’ alerts accepted by the AMS team (=number of APSS’ alerts accepted by the AMS team/number of alerts generated by APSS/month). So, analysis of sensitivity and specificity are not planned in this study, but implementation methods and secondary objectives will allow controlling imperfections of CDSS/ESS.
- The authors assumes that 12-months before / 12-months after observation period for first analysis is sufficient to account for seasonality. This could be questioned. They then report the willingness to conduct a secondary analysis using 24-month periods of observation. As the implementation date (2021?) of intervention is not reported, it is not possible to understand how this will be feasible. Please clarify this point. Will you observe the situation for 24 months, then implement the CDSS/ESS, then observe again…or did you plan to collect retrospective data for the 12-months and the 24-months period before the intervention starting (?) ? Procedures for collection of 12-months and 24-months data before intervention could be clarified.
We revised this part for a better understanding. In the “Outcomes Measures, Data Sources” section, we clarified: “The intervention is planned for 2022. Data for the before period will be collected retrospectively, while data for the after period may be collected prospectively.” We also revised the “Power and sample size calculations” section regarding the secondary analysis: “extended study which will cover a period of 24-month before and 24-month after the period during which the CDSS/ESS implementation will be performed at a later stage using the same outcomes.”

Reviewer 2 - Dr. Mah Laka, The University of Adelaide

Comments to the Author:
Thank you for the opportunity to review the protocol of a study which will assess the impact of CDSS and ESS on facilitating antibiotic stewardship and infection prevention and control activities. This study protocol is interesting providing clear outline of the study plan and analysis.
Dear Dr. Mah Laka, thank you for the reviewing of our manuscript and for your constructive comments.

My main concern is how the issue of alert fatigue will be handled in implementation. If excessive alerts are generated by APSS daily and especially during weekends which will be treated the next Monday - will there be a risk that AMS team have overwhelming amount of alerts to review?
Your concern is totally justified and very pragmatic because the use of APSS will likely increase the number of prescriptions revised daily by the AMS team. We revised our manuscript to explain more precisely the management of the alerts generated by APSS. In fact, the alerts are prioritized by APSS using rules which generate a score to target patients who are most in need of post prescription review. So, if the number of alerts is too high (in other words, if all the prescriptions could not be reviewed), the lowest levels of alert will not be reviewed.
Secondly, how will it be monitored that APSS recommendations are ignored/overridden or resulted in changes in prescriptions?
This information will be traced in APSS: for each alert, the AMS team will indicate whether the alert is overridden or considered clinically relevant or irrelevant.
Following are some of the minor concerns regarding this study protocol, which the authors may incorporate in the revised manuscript to improve the study quality:

- Introduction: A brief description/definition of CDSS and ESS would help readers understand the context of study. For example how ESS maximizes the effectiveness of IPC activities?
We have briefly described the functioning of CDSS and ESS for a better understanding.
- Objectives: One of the secondary outcomes is assess the safety of CDSS/ESS use on the incidence of certain HCAIs, but its not clear which certain HCAIs and how were they selected?
We clarified this point. The HCAI studied are the HCAI generating nosocomial epidemies and the HCAI caused by the five most frequent microorganism responsible of HCAI: Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa and Klebsiella pneumoniae (according to the French nationwide point-prevalence survey concerning HCAI).
For a better understanding and for the consistency of the text, we revised our manuscript in the "objectives" section, in the "setting and participants" section and in Table 1.
- Methods: The qualitative data collection is not sufficiently discussed. How many interviews will be conducted?
Regarding the qualitative study, we completed the "Outcomes Measures, Data Sources" section as follows: "Concerning the assessment of the users' satisfaction, a qualitative study based on individual and semi-directive interviews will be performed by an investigator (AB) with all the members of AMS and IPC teams who will use the software." Moreover, we completed the "qualitative analysis" section to explain that analysis will be performed by two investigators in order to realize a duplicate analysis of the qualitative data.

Reviewer 3 - Dr. L. E. Redding, Univ Penn

Comments to the Author:
This is a well-written manuscript with a comprehensively described protocol for evaluation of a stewardship intervention.
Dear Dr. L. E. Redding, thank you for the reviewing of our manuscript and for your constructive comments.

I do have some concerns about your implementation date. If the AMS and CDSS interventions were initiated in 2021, that means the year prior will have been 2020 and the year after part of 2021 and 2022. Do you anticipate that the covid pandemic will have altered antibiotic usage patterns and that therefore the pre- and post-years will not be comparable? Several studies (e.g., https://doi.org/10.3390/antibiotics10020182, https://doi.org/10.1017/ice.2020.381, https://doi.org/10.1080/23744235.2020.1839672, https://doi.org/10.1016/S1473-3099(20)30917-8 to name just a few) have shown very different patterns of antimicrobial prescribing during the pandemic, especially before vaccines became available. Where in your timeline does the implementation of this intervention fit? And how was the hospital affected by the pandemic? I see that you will consider the impact of the pandemic by eventually performing this analysis over a longer time period (24 months before and after), but you may want to say a bit more about whether this is sufficient and discuss how much you think the hospital and antibiotic prescribing may or may not have been affected by the pandemic.
Finally, the implementation date was postponed from 2021 to 2022. Then, the 12-month before period (year 2021) should be less affected by Covid-19, and we hope that the 12-month after period (year 2022) will be little/not affected by Covid-19 regarding antibiotic use. However, we will perform a preliminary study regarding Covid-19 impact on the antibiotic use in our hospital to take into account the possible variation during the different study periods. The results of this preliminary study will be used to improve the statistical analysis and to discuss the results of our study.
Specific comments:
- P6 L 46: please provide a bit more information on these comparable university hospitals. How many? Where located? Was it a representative sample?

We completed as follows: “In this nationwide point-prevalence survey, 25 University and Regional Hospitals were randomly select in France (including the University Hospital of Nancy) and constituted a representative sample.”
They were located in all French regions.
- P6 L 57-60: Why a random selection? Will the pre- and post-intervention patients be matched in some way? In particular, by indication for antibiotic therapy? If not, how do you ensure comparability?
We need to perform a random selection because the assessment will be performed manually by AMS and IPC team. Due to the wide number of patients receiving antibiotic and additional precaution prescriptions, it is impossible for these teams to review all the patient files to assess the appropriateness of the prescriptions.
The pre- and post-intervention patients will not be matched, but the randomization should ensure the representativeness and avoid a selection bias.
- P 9 L 56-60: please provide more information on the interview process beyond “they will be interviewed”. By whom? In what manner? Is there an interview guide you can share? Who will perform the interviews and the analyses?
We completed the “Outcomes Measures, Data Sources” section as follows: “Concerning the assessment of the users’ satisfaction, a qualitative study based on individual and semi-directive interviews will be performed by an investigator (AB) with all the members of AMS and IPC teams who will use the software”. Moreover, we completed the “qualitative analysis” section to explain that analysis will be performed by two investigators in order to realize a duplicate analysis of the qualitative data.
The interview guide cannot be shared for the moment, it will be published with the qualitative study.
Some clarification on parameters in Table 1 would be appreciated:
- How do you define an HCAI?
We have completed Table 1 with a footnote, and we have also completed our manuscript in the “objectives” section and in the “setting and participants” section for a better understanding.
The studied HCAI are defined as infections acquired by patients more than 48 hours after their admission to hospital (and not present or incubated at admission) and caused by one of the five most frequent microorganisms responsible of HCAI in French healthcare facilities: Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa and Klebsiella pneumoniae.
- “Proportion of the antibiotic prescriptions compliant with guidelines” and “Proportion of the additional precaution prescriptions compliant with hospital recommendations”: will these be evaluated by the software or manually by a person?
These will be evaluated manually by AMS and IPC team. We completed the table.
- Proportion of C. difficile. Why do you only consider patients treated with antibiotics? Patients not treated with antibiotics can also develop C. diff infection, especially if immunosuppressed or on gastric acid suppressors, and since it is a hospital-acquired infection often acquired from the hospital environment, you’d hope that the expected decrease in overall AMU associated with your intervention would result in decreased C diff infections in all patients, not just those treated with antibiotics. In fact, you could argue that if your intervention is to decrease AMU overall, you may have some patients who were not treated with antibiotics who previously might have been, and I would think you would want to capture these patients in your denominator.
You are right. Thank you very much for this comment. We revised your study protocol accordingly.
A few small grammatical errors here and there (this is just a sampling, check the manuscript thoroughly).
- P6 L 53: “Infectious disease physicians also meet daily [with] microbiologists”
We revised
- P 9 L 11 “excepted”
We revised

VERSION 2 – REVIEW

REVIEWER	Delory, Tristan Sorbonne Universite
REVIEW RETURNED	03-Feb-2022

GENERAL COMMENTS	I am very excited about reading your results.

REVIEWER	Laka, Mah The University of Adelaide, School of Public Health
REVIEW RETURNED	03-Feb-2022

GENERAL COMMENTS	Thanks for providing the opportunity to review the revision of this study protocol. The authors have appropriately addressed all the comments. I have nothing further to add and recommend accepting the manuscript for publication.

REVIEWER	Redding, L. E. Univ Penn
REVIEW RETURNED	23-Jan-2022

GENERAL COMMENTS	Thank you for addressing my concerns, and good luck with the study!